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EDITORIAL REVIEW

Current status of the use of $1,25(OH)_2D_3$ in the management of renal osteodystrophy

Renal failure is associated with many disturbances in the metabolism of divalent ions, and these abnormalities have been collectively called "renal osteodystrophy." They may include hypocalcemia, hyperphosphatemia, hypermagnesemia, skeletal resistance to the calcemic action of parathyroid hormone (PTH), defective intestinal absorption of calcium, secondary hyperparathyroidism and elevated blood levels of PTH, soft tissue calcification, and bone disease [1]. Many of these derangements could be the direct results or the consequences of vitamin D deficiency. For this reason vitamin D compounds have been used to treat some of these abnormalities [2–5]. It soon became obvious that very large doses of the vitamin are required to improve or correct certain components of renal osteodystrophy [2, 6, 7]. This phenomenon has led to the suggestion that a vitamin-D-resistant state exists in patients with uremia.

Recent advances in the field of vitamin D metabolism have shown that the parent vitamin undergoes several metabolic changes, resulting in the formation of biologically active metabolites [8–12]. The biologic activity of these metabolites has been studied with varying degrees of detail both in animals [11–14] and humans [15–18]. Most attention was given to the effects of 25-hydroxyvitamin D (25-OH-D_3) and 1,25 dihydroxyvitamin D ($1,25[OH]_2D_3$) [11–14] and more recently to 24,25 dihydroxyvitamin D ($24,25[OH]_2D_3$) [19, 20].

The most active vitamin D metabolite is $1,25(OH)_2D_3$, and it is made solely by the kidney [10, 21, 22]. Therefore, patients with chronic uremia and reduced functioning renal mass may not be able to produce an adequate amount of $1,25(OH)_2D_3$, and therefore, a state of vitamin D deficiency could develop. Indeed, the blood concentrations of $1,25(OH)_2D_3$ in patients with advanced renal failure and those treated with dialysis are either very low or undetectable [23]. These findings provided at least a partial explanation for the concept of a vitamin-D-resistant state in uremia and formed the basis for the therapeutic rationale for the use of $1,25(OH)_2D_3$ in the management of the abnormalities of divalent ion metabolism in patients with advanced renal failure.

Several lines of evidence indicate that a vitamin-D-deficient state may even exist in patients with early and moderate renal failure. First, skeletal resistance to the calcemic action of PTH, which is at least partly due to a deficiency in $1,25(OH)_2D_3$ [24], as demonstrated in nephrectomized dogs, is present in patients with early renal failure [25]. Second, impaired intestinal absorption of calcium could be demonstrated in patients with creatinine clearance of 50 to 80 ml/min [26]. The authors found that 6 of their 26 patients had low intestinal absorption of calcium. Third, defective mineralization of osteoid has been found in patients with a GFR greater than 50 ml/min [27]. It is interesting, however, that both Slatopolsky et al [28] and ourselves (unpublished observations) have found that the blood concentrations of $1,25(OH)_2D_3$ in such patients are either normal or mildly elevated. To reconcile between target organ evidence for vitamin D deficiency and normal blood concentrations of $1,25(OH)_2D_3$, one can conclude that a vitamin-D-resistant state is present, and supranormal blood concentrations of $1,25(OH)_2D_3$ are needed to maintain normal function of the target organs that require vitamin D for their metabolism. Indeed, dietary phosphate restriction [29], a procedure that may enhance the production of $1,25(OH)_2D_3$ by the kidney, raised the blood concentrations of $1,25(OH)_2D_3$ in such patients and was associated with reversal of the defects and abnormalities of the target organs (unpublished observations). The mechanisms of a vitamin-D-resistant state in patients with early renal failure and the reasons for the inability to raise their blood levels of $1,25(OH)_2D_3$ are complex and not yet understood.

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These findings provide a rational basis for the initiation of $1,25(OH)_2D_3$ therapy early in the course of renal insufficiency. At present, the drug is not available for use in such patients, and its clinical efficacy in patients with early renal failure needs to be demonstrated by future investigation (see below).

It is important to emphasize at this point that some or most of the beneficial effects of $1,25(OH)_2D_3$ in the management of renal osteodystrophy could be produced by other vitamin D compounds, such as cholecalciferol [3, 30], dihydrotachysterol [2, 5], or 25-OH-D_3 [15, 16]. The smaller dose of $1,25(OH)_2D_3$ that is needed to achieve beneficial effects and its shorter half life make it, however, a better and a safer agent than are the other compounds. On the other hand, the high biologic potency of $1,25(OH)_2D_3$ causes the early appearance of hazardous side effects with even very small doses. Thus, close monitoring of the patients receiving $1,25(OH)_2D_3$ is mandatory.

A large number of studies have been performed evaluating the effects of $1,25(OH)_2D_3$ on divalent ion metabolism in patients with advanced renal failure and those treated with hemodialysis. These reports describe varying degrees of success in the management of the different components of renal osteodystrophy. These variations may be related to differences in the pathologic lesions among the patients, the dose of the metabolite, the duration of therapy, and the methods of assessment. Because $1,25(OH)_2D_3$ is now available for general use in the treatment of renal osteodystrophy in dialysis patients, it appears timely to review the available information on its effects and hazards in order to provide a critical analysis of the basis for its therapeutic use.

The information in this editorial is based on data published from November, 1972 (the first report on clinical use of $1,25(OH)_2D_3$), through July, 1979, and it includes 30 reports [17, 18, 31–58]. These data describe the effects of $1,25(OH)_2D_3$ in 57 patients with chronic uremia and 208 dialysis patients. There were 28 children among this patient population. We emphasize, however, that the actual number of patients studied could be smaller because some patients may have been reported more than once. A symposium dealing with the clinical use of $1,25(OH)_2D_3$ was held in Chantecler, Quebec, Canada, June, 1978. During this symposium, the investigators described their experiences with this vitamin D metabolite. The reader is referred to the proceedings of this symposium [59].

Dosage

The dosage of $1,25(OH)_2D_3$ varied from 0.027 to 3.0 μg/day. The dosage in the early studies was very small (< 0.5 μg/day), but recently most investigators have been initiating therapy with 0.5 μg/day and increasing the dosage, thereafter. Because hypercalcemia has been reported occasionally with 0.5 μg/day or less [18, 43, 49], it may be safer to start therapy with 0.25 μg/day. The effects of $1,25(OH)_2D_3$ on target organs such as the gut or the bone provide the best criteria for the adjustment of the dose, but it is not feasible from a practical standpoint to evaluate the changes in intestinal calcium absorption or bone histology on a repeated and frequent basis. Therefore, it appears that the changes in concentrations of serum calcium can provide an alternative guide for the modification of therapy. Failure to elevate serum calcium concentration by at least 0.5 mg/dl with any particular dosage given for 4 to 6 weeks justifies increasing the dosage by 0.25 to 0.5 μg/day. Such an approach may be used until serum calcium reaches the normal range (10.0 to 10.5 mg/dl). When this is achieved, frequent monitoring of serum calcium is needed, and if the latter approaches the hypercalcemic range, a reduction of the dose or temporary discontinuation of therapy should be considered. It is our experience and that of others [36, 39, 49, 58] that the requirement of and the tolerance to $1,25(OH)_2D_3$ may decrease progressively during treatment in many patients; therefore, reduction of the maintenance dosage after a prolonged period of therapy may be needed.

As many patients with chronic renal failure have hyperphosphatemia [1], and as the concentration of serum phosphorus may increase during therapy with $1,25(OH)_2D_3$, it is mandatory to maintain serum phosphorus concentrations within the normal range. At no time should the calcium-phosphorus product in blood exceed 55.

Clinical signs and symptoms

Among the most disturbing clinical symptoms of renal osteodystrophy are muscle weakness [60, 61], and bone pain [62]. The muscle weakness is a clinical manifestation of uremic myopathy, which is probably due to vitamin D deficiency [61]. The exact cause of bone pain in the uremic patients is not known, but may be related to the presence of osteomalacia and/or osteitis fibrosa. These disturbances may interfere seriously with the daily activity of the patients and may even render them totally disabled.

Improvement in these symptoms appears rapidly after initiation of therapy with this metabolite. Coburn et al [41] reported that skeletal pain began to improve within 1 to 3 weeks of therapy and that it disappeared in half of their symptomatic patients. In addition, the majority of their patients showed improvement in muscle strength. Pierides et al [35] found that treatment with 1,25(OH)$_2$D$_3$ improved muscle strength and decreased bone pain. We also evaluated the effect of the sterol on these symptoms in 15 patients [49]. They displayed improvement in muscle strength after 2 to 5 weeks of treatment, but it took 6 to 28 weeks of therapy before a decrease in bone pain became apparent. Thirteen of our patients had various degrees of physical disability, and within 6 to 18 months, 11 of them became free of symptoms and were able to pursue their daily physical activity. It should be emphasized that prolonged therapy may be required in some patients before such a remarkable improvement in physical activity occurs. Similar observations were reported in children [42, 45, 54]. Chesney et al [54] found that 9 of their 11 patients showed marked improvement in muscle strength. They described 3 children who had ceased walking for sevearl months prior to therapy, who began walking within 1 month and were running within 4 months of treatment.

Another important effect of 1,25(OH)$_2$D$_3$ in uremic children is the increase in growth velocity. Chesney et al [54] found that height velocity in 8 of 9 uremic children improved markedly during therapy with the sterol. The height velocity was in the third percentile before therapy and rose to the 10th to 97th percentile after several months of treatment. These data assign an important role for the use of 1,25(OH)$_2$D$_3$ in uremic children, as retarded growth is a very common and serious problem in these patients [63, 64].

Serum calcium concentration

The most consistent effect of 1,25(OH)$_2$D$_3$ in the uremic and dialysis patients is the elevation in the serum concentration of calcium [17, 18, 31, 36, 39–43, 45, 46, 48, 49, 51–54, 56, 58]. Brickman et al [17] reported the effects of three dosages of the metabolite (0.14, 0.68, and 2.7 μg/day) given for 7 to 15 days to 10 patients. They demonstrated a significant rise in serum calcium in the patients receiving 0.68 or 2.7 μg/day. The data of other investigators confirm these observations [18, 31, 32, 36, 39–43, 45, 46, 48, 49, 51–54, 56, 58] and indicate that most patients will display a rise in serum calcium after treatment with 0.5 μg/day within 5 days to 4 weeks [41, 43, 45, 51, 52]. Although it is reasonable to assume that the higher the dosage of the metabolite the greater the rise in serum calcium concentration, the available data do not permit an evaluation of a dose-response curve. Furthermore, many variables in addition to the dose may modify the calcemic response to therapy with 1,25(OH)$_2$D$_3$. These may include duration of treatment, dietary calcium intake, changes in intestinal absorption of calcium, type of bone disease and its response to treatment, and the severity of the state of secondary hyperparathyroidism. Occasionally, the serum calcium concentration may fall during the first 1 to 2 weeks of therapy, probably due to rapid remineralization of the skeleton; Brickman et al reported 3 such patients [53].

Hypercalcemia is a frequent complication of treatment with 1,25(OH)$_2$D$_3$. It has been reported that 30 to 67% of the patients treated with this metabolite developed one or more hypercalcemic episodes during the course of their therapy. The overall incidence of one episode was 42%. Hypercalcemia occurred with a dosage of 0.5 to 3.0 μg/day of 1,25(OH)$_2$D$_3$ but was more frequent with dosages of 1.0 to 3.0 μg/day. Certain patients are more prone to develop hypercalcemia. They include: *(1)* patients with osteitis fibrosa and pretreatment serum calcium concentrations greater than 10.5 mg/day; in one such patient, treatment with a very small dosage of 0.14 μg/day for 2 weeks produced severe hypercalcemia (14.5 mg/dl) [18], and *(2)* patients with "pure" osteomalacia, low serum concentrations of PTH and absent bone marrow fibrosis [41]. Coburn et al [65] reported that all 9 patients who had "pure" osteomalacia developed hypercalcemia with dosages of less than 0.5 μg/day.

Hypercalcemia may appear at any time during therapy with 1,25(OH)$_2$D$_3$. It usually occurs after 2 to 3 months of therapy but has been reported as early as 5 days [34] and as late as 6 to 18 months after treatment. Hypercalcemia has been reported 5 [34] and 6 [31] days after initiation of therapy with large initial dosages of 2.0 and 2.7 μg/day, respectively. The high starting dose may have been the cause for the early appearance of hypercalcemia. It is advisable, therefore, to initiate therapy with small doses of 1,25(OH)$_2$D$_3$ of 0.25 or 0.50 μg/day. Early hypercalcemia within 1 to 4 weeks of therapy may also occur in patients with severe osteitis fibrosa and pretreatment serum calcium concentrations of

10.5 mg/dl. Extreme caution should be exercised in the management of such patients with $1,25(OH)_2D_3$.

It has been noted that the incidence of hypercalcemia increases as the serum alkaline phosphatase activity returns to normal [41, 49, 53], and it is recommended to reduce the dosage of $1,25(OH)_2D_3$ when serum alkaline phosphatase activity normalizes.

The hypercalcemia is usually mild and asymptomatic [17, 18, 32, 34-36, 41, 43, 45, 46, 49, 51, 54], but serum calcium concentrations greater than 13.0 mg/dl [18, 49] and occasionally even higher than 15.0 mg/dl have been encountered during therapy with $1,25(OH)_2D_3$ [56]. The reported data indicate that serum calcium concentrations returned to normal after reduction of the dosage or cessation of therapy. Occasionally, hypercalcemia may persist for several weeks after discontinuation of treatment, and two such patients required subtotal parathyroidectomy for the control of the hypercalcemia [18, 39]. The available information indicates that it is advisable to stop treatment completely rather than reduce the dosage when hypercalcemia appears and reinstitute therapy with a smaller dose as serum calcium concentrations return to normal.

Serum phosphorus concentration

The effect of $1,25(OH)_2D_3$ treatment on the concentration of serum phosphorus in uremic or dialysis patients is not consistent. An increase, a decrease, or no change have been reported [18, 31-34, 36, 39-41, 43, 45, 46, 48, 49, 51-54, 56, 58]. This variability in the various patient populations may be related to differences in dietary intake of phosphorus and/or the ingestion of phosphate binding antacids, the dosage of $1,25(OH)_2D_3$, the effect of the metabolite on intestinal absorption of phosphorus, the degree of suppression of the parathyroid gland activity, and the status of the remineralization of bone. Monitoring of serum phosphorus concentrations during therapy with $1,25(OH)_2D_3$ is mandatory because the development of hyperphosphatemia, especially in the face of rising serum calcium concentration, would result in elevation of the calcium-phosphorus product and augment the hazards of soft tissue calcification. If hyperphosphatemia occurs and the calcium-phosphorus product approaches 55, every effort should be made to control serum phosphorus with phosphate-binding antacids. If this procedure is not successful, the dose of $1,25(OH)_2D_3$ should be reduced or temporary cessation of therapy should be considered.

Serum alkaline phosphatase activity

Serum alkaline phosphatase activity usually decreases during therapy with $1,25(OH)_2D_3$, but several months may elapse before the level returns to normal [18, 35, 36, 41-43, 45, 59, 52-54, 58] (Fig. 1). We have encountered patients in whom the alkaline phosphatase activites remained elevated for 10 to 14 months and began to fall only after the administration of large dosages of the metabolite (1.5 to 2.5 μg/day). Occasionally, serum alkaline phosphatase may rise during the initial phase of

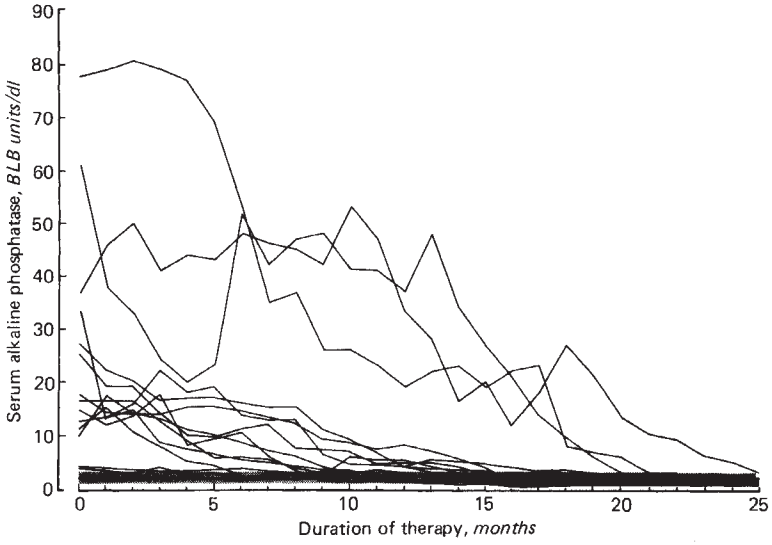

Fig. 1. *Changes in serum alkaline phosphatase activities in 15 dialysis patients during therapy with $1,25(OH)_2D_3$ for up to 25 months.* Shaded area represents normal values.

therapy. Monitoring of serum alkaline phosphatase could provide an additional guide for the adjustment of the dosage of 1,25(OH)$_2$D$_3$ for two reasons. First, normalization of serum alkaline phosphatase reflects improvement in bone disease, and second, the occurrence of hypercalcemia increases as serum alkaline phosphatase returns to normal.

Serum PTH level

The effect of 1,25(OH)$_2$D$_3$ on serum levels of PTH has been reported in about 120 patients treated with 0.25 to 3.0 μg/day and for periods of 3 weeks to 18 months [18, 35, 39, 43–46, 48, 49, 51–54]. The serum levels of PTH decreased by 13 to 90% of the control values in most patients, and in few (30 patients) the serum levels returned to normal. No change or an increase in serum PTH concentration was also reported [39, 44, 49, 51, 54]. The variability in these results may be related to differences in basal serum levels of PTH reflecting the degree of hyperplasia of the parathyroid glands, the day to day fluctuation of serum PTH levels, the dosage and duration of therapy, the magnitude of rise in serum calcium, and the type of PTH assay.

Binswanger et al [51] made simultaneous measurements of both the C- and the N-terminal fragments of PTH during therapy with 1,25(OH)$_2$D$_3$. They found that the effect of the metabolite on serum PTH levels is better evaluated by the N-terminal fragment because a significant decrease in the concentration of this moiety occurred without a significant change in the levels of the C-terminal fragment. Both Bordier et al [44] and we [49] reported marked fluctuations in serum levels of PTH during therapy with 1,25(OH)$_2$D$_3$, and it is evident, therefore, that single measurements of serum PTH levels before and after therapy may provide misleading results.

The reduction in the serum levels of PTH during therapy with 1,25(OH)$_2$D$_3$ is probably due to the rise in the concentration of serum calcium. We [49] found an inverse correlation between the percent change in serum calcium concentrations and PTH levels (Fig. 2). Binswanger et al [51] and Brickman et al [53] could also demonstrate that the fall in serum PTH levels was related to the rise in serum calcium concentrations in many of their patients. It is also possible that 1,25(OH)$_2$D$_3$, itself, directly suppresses the parathyroid gland activity. The available data in this regard are conflicting and have been reviewed recently in detail by Golden et al [66].

Intestinal calcium and phosphorus absorption and urinary calcium

Intestinal calcium absorption increased in most patients during therapy with 1,25(OH)$_2$D$_3$ [17, 30–33, 35, 37–43, 47, 49, 51]. The effect of the sterol on this parameter was carefully evaluated by Brickman et al [67], who found the following: *(1)* The increment in calcium absorption was most evident during the first 2 hours after the ingestion of the calcium 47, suggesting that the metabolite exerts its effect in the duodenum and proximal part of the small intestine. It should be mentioned that Wecksler, Mason, and Norman [68] demonstrated specific cytosol receptors for 1,25(OH)$_2$D$_3$ in the human jejunum and, therefore, the sterol may enhance calcium absorption in this segment of the intestine as well. *(2)* There is a dose-response relationship between 1,25(OH)$_2$D$_3$ and intestinal absorption of calcium. *(3)* The quantity of the sterol required to elicit an increase in intestinal calcium absorption in the uremic patient is greater than it is in normal subjects [17]; this observation suggests that uremia may interfere with the action of the sterol on the gut.

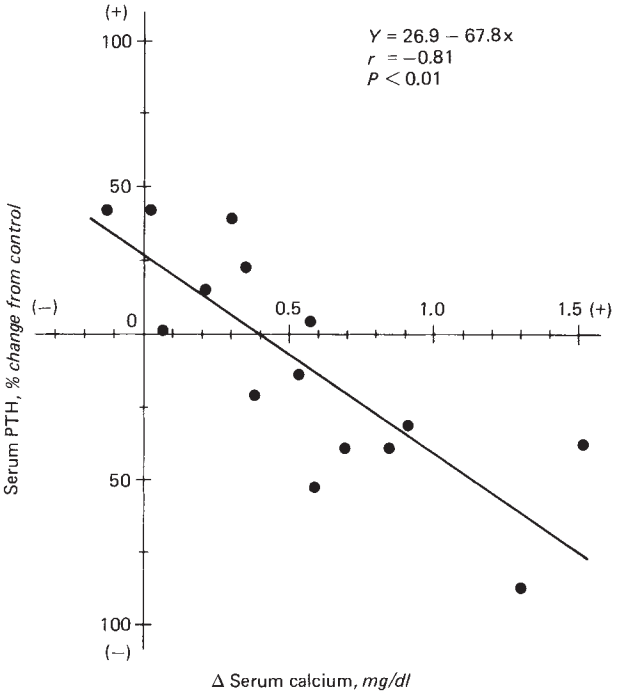

Fig. 2. *Relationship between the changes in the concentration of serum calcium and the percent change in serum iPTH levels during therapy with 1,25(OH)$_2$D$_3$.* Each data point represents 1 patient. From Goldstein et al [49].

The mechanisms through which $1,25(OH)_2D_3$ enhances intestinal absorption are complex [69], and it has been suggested that the sterol augments the synthesis of a calcium-binding protein, which facilitates the transport of calcium across the gut [70]. Our studies [71] showed that uremic patients have structural abnormalities of the duodenal mucosa, including a decrease in the length of the villi and the crypt of Lieberkühn and distortion of the microvilli. The treatment with $1,25(OH)_2D_3$ restored the structural integrity of the duodenal mucosa. These derangements may contribute to the defect in calcium absorption through the reduction of the absorptive surfaces and interfere with their function.

Brickman et al [40] also studied, with metabolic balance techniques, the effect of $1,25(OH)_2D_3$ on intestinal phosphorus absorption in a few uremic patients. They found the net intestinal absorption of phosphorous is augmented during treatment with 0.14 to 2.7 μg/day of $1,25(OH)_2D_3$ for 6 to 15 days. The increase in net phosphorus absorption ranged from 0.6 to 12.0 (3.9 ± [SEM] 0.82) mmoles/day. Interestingly, these authors found a significant correlation between net intestinal absorption of phosphorus and that of calcium. This effect of $1,25(OH)_2D_3$ is most probably responsible, at least partly, for the rise in the concentration of serum phosphorus that may occur in many uremic patients treated with this sterol.

The effect of $1,25(OH)_2D_3$ on urinary calcium has been studied in few patients with advanced renal failure [17, 32, 33, 48] and in three patients with moderate renal failure [72]. There were either no changes or modest increments of 20 to 110 mg/day in urinary calcium excretion.

Bone disease

The effects of $1,25(OH)_2D_3$ on bone histology have been evaluated in 105 patients [18, 33, 35, 36, 38, 42–44, 46, 50, 51, 54, 55, 58, 73]. It is difficult, however, to accurately interpret these data for several reasons. First, many of the investigators used qualitative or semiquantitative methods, and others did not report their results in detail. Second, the changes in bone histology observed after therapy may not be entirely due to $1,25(OH)_2D_3$ but may reflect the considerable variability in bone histology that exists at various sites of the skeleton [73]. To overcome this problem, one should obtain two bone specimens before treatment to evaluate the intrinsic variability of skeletal histology; differences between pretreatment and posttreatment values could be attributed to therapy with $1,25(OH)_2D_3$ only when they are significantly greater than the variance between the two biopsy specimens obtained prior to treatment. Third, the diagnosis of osteomalacia and the assessment of bone mineralization were made in most patients (68/93 patients) without double tetracycline labeling, which is considered the most appropriate technique for the evaluation of osteomalacia and bone mineralization [74].

Despite these limitations, a pattern on the effect of $1,25(OH)_2D_3$ emerges from these studies. It appears that therapy with this metabolite for several months could be associated with a decrease in bone resorption [18, 35, 38, 42–44, 50, 55, 58, 73]. Such an effect was not universal, however [43, 44, 46, 50, 73], and only in a few patients did bone resorption return to normal [18, 43, 50]. This is not surprising because such an effect of the metabolite is mediated through the reduction in the serum levels of PTH, which have been found to return to normal levels only in a small percentage of the patients. Endosteal fibrosis was either markedly reduced or even disappeared during therapy with $1,25(OH)_2D_3$ [18, 35, 44, 50], irrespective of whether the serum levels of PTH were decreased or not [50]. This finding raises the possibility that endosteal fibrosis is not entirely the result of excess PTH but could also be related to vitamin D deficiency as well.

The data on the effects of $1,25(OH)_2D_3$ on uremic osteomalacia are variable. Coburn et al [65] reported that therapy with this sterol failed to exert a beneficial effect on bone in patients with pure osteomalacia and normal serum levels of PTH. Delling et al [55] also reported no improvement in histologic parameters in patients with osteomalacia and no evidence of hyperparathyroid bone disease. On the other hand, other investigators reported improvement [35, 38, 42, 43, 46, 52, 55, 58, 73] or healing [38, 50] of osteomalacia in patients who displayed evidence of both osteomalacia and enhanced bone resorption. In a study of 12 such patients, we [50], using double tetracycline labeling, found that osteomalacia healed in 7, improved in 3, and did not change in 2 patients after 6 months of treatment.

Bone x-rays and bone mineral contents

The changes in radiographic appearance of bone disease during therapy with $1,25(OH)_2D_3$ have been evaluated in a limited number of patients. Evidence for healing of renal rickets in children [42, 54], or of osteomalacia in adults as demonstrated by the disappearance of pseudofractures [33, 36], has been noted. The effects on the x-ray manifestations of hyperparathyroidism were also evaluated. We [49]

examined the radiographs of the skull and hands in 10 patients before and after 6 months of therapy. Four patients showed improvement in the radiographic changes in the skull without concomitant improvement in those of the hands; in these patients the serum levels of PTH fell. In two patients who displayed worsening of the radiographic findings, serum levels of PTH rose. In the remaining four patients, the changes in x-rays remained unaltered. Berl et al [46] found that only 1 of their 15 patients showed improvement in x-ray signs of bone resorption after therapy for 3 months.

Only three groups studied the effect of $1,25(OH)_2D_3$ on bone mineral content (BMC) in a total of 23 patients with densitometry [36, 51, 54]. Improvement in BMC was reported in 6 patients [36, 54], 5 of them were children [54]. All of these patients had overt signs and symptoms of renal osteodystrophy. On the other hand, Binswanger et al [51] found no change in BMC in 17 dialysis patients, without symptomatic bone disease, treated with 0.2 to 1.0 μg/day $1,25(OH)_2D_3$ for 3 to 8 months.

Although the data on bone x-rays and BMC suggest that these techniques are not valuable tools for the assessment of the effectiveness of therapy with $1,25(OH)_2D_3$, the paucity of the information does not allow a definite conclusion in this regard.

Treatment failure

Failure of therapy with $1,25(OH)_2D_3$ to improve clinical signs and symptoms has been reported [41, 53, 75], and, in one study, this was attributed to hypophosphatemia [76]. Coburn et al [41] reported that 11 of 38 patients failed to improve their clinical symptoms; this could not have been due to hypophosphatemia, because the serum concentrations of phosphorus were not low. The treatment-failure group appears to be heterogenous and does not display a specific biochemical pattern or bone disease. Although they had higher serum calcium concentrations than did those who responded to treatment, the serum levels of PTH were normal, moderately elevated, or very high, and the bone lesions varied from pure osteomalacia in some to marked osteitis fibrosa in others. Further analysis of the data, however, indicates that there are two distinct subgroups among these patients.

The first group consists of patients with severe osteitis fibrosa and marked elevation of serum PTH. In the second group, the patients had normal serum levels of PTH and pure osteomalacia without evidence of hyperparathyroid bone disease [41, 53, 65], a combination that is difficult to explain unless these patients have failure of parathyroid gland activity and vitamin D deficiency as well. Coburn et al [65] reported 10 such patients, but the incidence of this disease in the American uremic population is not established. Delling et al [55] reported 12 similar patients and claimed that the incidence of pure osteomalacia in the European uremic population may be 20 to 30% [77]. Kanis et al [58] also encountered patients with similar bone lesions and failure to respond to therapy with $1,25(OH)_2D_3$.

Both of these groups rapidly developed hypercalcemia. As this complication requires cessation of treatment, it would preclude long-term therapy and, hence, failure to improve the clinical and histologic abnormailties of renal osteodystrophy. Other mechanisms, however, could be responsible for the treatment failure in the patients with pure osteomalacia, because Coburn et al [41] continued the treatment of these patients despite mild hypercalcemia and found no healing of the bone lesions. They postulated that the low bone turnover is of paramount importance in the failure of therapy. It is possible that the healing of the pure osteomalacia requires other vitamin D metabolites such as 25-OH-D_3 or $24,25(OH)_2D_3$ in addition to $1,25(OH)_2D_3$.

Effects in patients with moderate renal failure and on GFR

Data on the effect of $1,25(OH)_2D_3$ on the derangements of divalent ion metabolism in patients with moderate renal failure are limited. Healey et al [72] treated three patients with creatinine clearances of 32, 49, and 51 ml/min with 0.5 μg/day of $1,25(OH)_2D_3$ for 6 months. They found that this therapy raised serum calcium, reversed the defect in intestinal calcium absorption, normalized the serum levels of PTH, and healed the bone disease. These observations suggest that initiation of therapy with $1,25(OH)_2D_3$ at the early course of renal failure could be beneficial for the prevention of the progression of renal osteodystrophy. Such an approach could be justified, however, if treatment with this metabolite has no harmful effect on renal function.

Theoretically, a deleterious effect of $1,25(OH)_2D_3$ on renal function could be due to a direct action of the metabolite on the structure or function of the kidneys or due to other metabolic consequences of the treatment such as hypercalcemia. Christiansen et al [48] claimed that the administration of $1,25(OH)_2D_3$ to patients with moderate renal failure produced a significant reduction in GFR from 25.8

± 11.5 to 20.1 ± (SD) 12.8 ml/min. They attributed this change to a direct effect of the metabolite on kidney function. Serious questions could be raised regarding the significance of their results and the validity of their conclusions. First, the decrease in the creatinine clearance in the patients receiving $1,25(OH)_2D_3$ was not significantly greater than it was in patients treated with 100 μg/day of vitamin D_3. Second, they did not perform frequent and sequential measurements of creatinine clearance during the therapy period, and they relied on a single determination made at the end of the treatment; such an approach may lead to false conclusions, for creatinine clearance fluctuates widely from day to day. Third, 7 of their 8 patients developed hypercalcemia, and this complication might have contributed to the decrease in creatinine clearance. We have measured creatinine clearance every 2 weeks during 6 months of therapy with $1,25(OH)_2D_3$ in patients with moderate renal failure [72]. Hypercalcemia did not occur, and GFR remained stable. Our results and other pertinent data recently reviewed [78] do not support the contention that $1,25(OH)_2D_3$ has a direct deleterious effect on renal function. The metabolite could produce a reversible or permanent fall in GFR, however, if sustained hypercalcemia develops during its administration. The use of the proper dosage, the frequent monitoring of serum calcium and creatinine concentrations, and the discontinuation of therapy as hypercalcemia develops are the precautionary measures that should be followed to reduce the likelihood of a harmful effect on renal function.

Although the data of Healey et al [72] suggest that 0.5 μg/day of $1,25(OH)_2D_3$ is beneficial and safe in patients with GFR's of 30 to 51 ml/min and normophosphatemia, it is possible that smaller or larger dosages may be required by patients with higher or lower creatinine clearance, respectively. Caution should be exercised in the use of $1,25(OH)_2D_3$ in patients with GFR's less than 25 ml/min. These patients may be hyperphosphatemic, and a rise in blood calcium concentration in the presence of elevated blood phosphorus concentration would result in an increase in the calcium-phosphorus product to a hazardous level. In such an eventuality, calcium deposition may occur in various tissues, including the renal parenchyma. The latter effect could be associated with deterioration in renal function.

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